Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma.

Bibliographic Source(s)

American Society for Blood and Marrow Transplantation. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma. Biol Blood Marrow Transplant. 2011 Feb;17(2):190-1. PubMed

Oliansky DM, Gordon LI, King J, Laport G, Leonard JP, McLaughlin P, Soiffer RJ, van Besien KW, Werner M, Jones RB, McCarthy PL Jr, Hahn T. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. Biol Blood Marrow Transplant. 2010 Apr;16(4):443-68. [85 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The levels of evidence (1++ to 4) and the grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

The following treatment recommendations are offered for the role of stem cell transplantation (SCT) as treatment for follicular lymphoma (FL), and are based on consensus reached by an expert panel following a systematic review of the literature.

Autologous SCT versus Non-transplantation Therapy

1. Based on pre-rituximab data, there is a statistically significant improvement in overall survival (OS) and progression-free survival (PFS) using autologous SCT as salvage therapy. (Grade of Recommendation A, Highest Level of Evidence 1-)
2. With only one retrospective study, there are insufficient data to make a recommendation on the use of autologous SCT versus non-transplantation therapy as salvage treatment for patients who have had rituximab as part of their salvage therapy. (No Recommendation, Highest Level of Evidence 2+)
3. Autologous SCT is recommended for transformed FL based on expert opinion and accepted clinical practice. (Grade of Recommendation D, Highest Level of Evidence 3)
4. Although there is consistent improvement in PFS and event-free survival (EFS) with autologous SCT, it is not recommended as first-line treatment for most patients because of no significant improvement in OS, a higher incidence of secondary myelodysplastic syndrome (MDS)

and acute myeloid leukemia (AML), and a lack of comparative data with rituximab-containing regimens. Longer follow-up may be needed to identify differences in OS. (Grade of Recommendation A, Highest Level of Evidence 1++)

Autologous SCT: Timing and Protocol

1. There are insufficient data to make a recommendation on the efficacy of autologous SCT as first-line versus salvage therapy. (No Recommendation, Highest Level of Evidence 2-)
2. Because of conflicting data, a recommendation cannot be made on the use of rituximab as part of first line or salvage regimens prior to autologous SCT. (No Recommendation, Highest Level of Evidence 2-)
3. There are insufficient data to make a recommendation regarding purging of autologous SCT. (No Recommendation, Highest Level of Evidence 1-)
4. There are insufficient data to recommend one high-dose regimen over another. Total-body irradiation (TBI)-containing regimens are usually avoided because of a concern for the risk of secondary MDS or AML. (No Recommendation, Highest Level of Evidence 2+)

Autologous versus Allogeneic SCT

1. There are insufficient data comparing autologous SCT and myeloablative allogeneic SCT to recommend one option over the other; both appear to have a survival benefit, but have competing risks. Comparison of these two techniques is biased by different patient selection criteria. (No Recommendation, Highest Level of Evidence 2+)
2. There are currently no data available to make a recommendation regarding the use of reduced intensity/nonmyeloablative allogeneic SCT versus autologous SCT. Comparison of these two techniques is biased by different patient selection criteria. (No Recommendation, No Evidence Available)

Allogeneic SCT: Conditioning and Donor Source

1. Reduced intensity conditioning (RIC) appears to be an acceptable alternative approach in allogeneic SCT based on one study and expert opinion. (No Recommendation, Highest Level of Evidence 2++)
2. There are insufficient data to recommend one conditioning regimen over another for allogeneic SCT. (No Recommendation, Highest Level of Evidence 2++)
3. In allogeneic SCT, a human leukocyte antigen (HLA)-matched unrelated donor appears to be as effective as an HLA-matched related donor using RIC based on expert opinion. (No Recommendation, Highest Level of Evidence 4)

Definitions:

Grading the Quality of Design and Strength of Evidence

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-controlled or cohort studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case controlled or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2-	Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Non-analytic studies (e.g., case reports, case series)
4	Expert opinion

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Follicular non-Hodgkin lymphoma

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Hematology

Internal Medicine

Oncology

Radiation Oncology

Intended Users

Health Care Providers

Health Plans

Physicians

Guideline Objective(s)

- To assemble and critically evaluate all valid, peer-reviewed evidence regarding the role of cytotoxic therapy with hematopoietic stem cell

transplantation (SCT) in the therapy of follicular lymphoma
- To provide treatment recommendations based on the available evidence
- To identify discrepancies in study design or methodology among published studies that may impact the quality of the evidence
- To identify areas of needed research

Target Population

Follicular lymphoma (FL) patients ≥15 years of age

Interventions and Practices Considered

1. Autologous stem cell transplantation (SCT) versus non-transplantation therapy
2. Autologous SCT: timing and protocol
3. Autologous versus allogeneic SCT
4. Allogeneic SCT: conditioning and donor source

Major Outcomes Considered

- Disease-free, progression-free, event-free, relapse-free, and overall survival
- Treatment-related mortality
- Incidence of myelodysplastic syndrome and acute myelogenous leukemia

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

PubMed and Medline, the Web sites developed by the National Center of Biotechnology Information at the National Library of Medicine of the National Institutes of Health, were searched on June 10, 2008, using the search terms "follicular lymphoma" and "transplantation" limited to "human trials," "English language," and a publication date of 1990 or later. Updated searches were conducted on January 12, 2009, and June 9, 2009. In addition to the online database searches, a manual search of the reference lists of reviews and included articles was conducted. Papers published before 1990, that included fewer than 25 follicular lymphoma (FL) patients, or were not peer reviewed were excluded. Also excluded were editorials, letters to the editor, Phase I (dose escalation or dose finding) studies, reviews, consensus conference papers, practice guidelines, and laboratory studies with no clinical correlates. Abstracts and presentations at national or international meetings were not included as evidence in this review for reasons previously described. To be included in this evidence-based review, at least 65% of a study's patients had to have FL, unless the results were stratified by histologic subtype of lymphoma.

Number of Source Documents

246

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading the Quality of Design and Strength of Evidence

Levels of Evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-controlled or cohort studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case controlled or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2-	Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Non-analytic studies (e.g., case reports, case series)
4	Expert opinion

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Qualitative and Quantitative Grading of the Evidence

The hierarchy of evidence, including a grading system for the quality and strength of the evidence and strength of each treatment recommendation (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields) define criteria used to grade the studies that were included in this review and criteria to grade the treatment recommendations, respectively. Study design, including sample size, patient selection criteria, duration of follow-up, and treatment plan also were considered in evaluating the studies. Clinical studies are described in the review's text and tables with sufficient detail to give a concise summary of study design, sample size, eligibility criteria, treatment schema, and patient outcomes.

All data in the text and tables were abstracted from the original manuscripts by the first author, and double-checked for accuracy and clarity by two other authors. Some articles contained inconsistencies within the data reported; the data most consistent with the text of the article were included in this review. The authors take responsibility if errors remain.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Society for Blood and Marrow Transplantation (ASBMT) in 1999 began an initiative to sponsor evidence-based reviews of the scientific and medical literature for the use of hematopoietic stem cell transplantation (SCT) in the therapy of selected diseases.

Expert Panel Selection

To achieve an appropriate balance, disease-specific experts who have published studies using SCT and other therapies are invited to join the independent expert panel that examines the literature and provides subsequent treatment recommendations based on the available evidence. For the current evidence-based review, potential panelists were considered based on their expertise in follicular lymphoma treatment. Potential panelists are restricted to U.S.-based institutions for 2 reasons: (1) ease of logistics in convening teleconferences, and (2) differences in the health care systems and health insurance coverage between the United States and other countries (including Canada, Europe, etc.) that may result in different expert recommendations based on considerations of costs and access to care.

Consensus Process

The Treatment Recommendations Table (Table 3 in the evidence-based review) contains the summary of consensus treatment recommendations made by the expert panel based on the summarized evidence. The consensus process involves a teleconference during which panelists critically discuss the evidence for each section of the review and develop initial treatment recommendations according to specified categories. The information is summarized by the primary authors and distributed to the panelists for additional review and clarification. Any changes suggested by an individual panelist are circulated for review and approval by all panelists. This iterative process concludes when a final version of the Treatment Recommendations table is approved by all panelists.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Source: Harbour R, Miller J. A new system for grading recommendations in evidence-based guidelines. *Br Med J*. 2001;323:334-336.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

After the final draft of the review is approved by the disease-specific expert panel, it undergoes peer review, first by the American Society for Blood and Marrow Transplantation (ASBMT) Steering Committee for Evidence-Based Reviews, then by the ASBMT Executive Committee before submission to the journal. Any changes requested during the peer-review process must be reviewed and approved by all disease-specific

expert panelists.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in adult patients with follicular lymphoma

Potential Harms

Toxicity of treatment

Qualifying Statements

Qualifying Statements

Study Limitations

- The strengths of this systematic evidence-based review are the details conveyed in the text about each study's design, the presentation of outcomes in summary tables for each major section, and the treatment recommendations made by the follicular lymphoma (FL) expert panel. A limitation is the exclusion of non peer-reviewed data. Unpublished data can represent "negative" findings that could lead to publication bias; however, the inclusion of high-quality, peer-reviewed publicly available data was of paramount importance. Data published in abstract form were not included because of the inadequate details of study design or patient characteristics, making a true assessment of the widespread applicability or impact of the treatment outside the scope of the trial difficult.
- A limitation of the FL literature is that there is no consistency in the survival estimate time points, making it difficult to compare outcomes across studies. FL is an indolent disease requiring long follow-up intervals; however, longer follow-up leads to delayed publication, making it problematic to reflect up-to-date information. Although many studies in this review reported short (<5 years) follow-up intervals, much of the evidence presented in this review does not reflect current clinical practice. For example, most of the reviewed studies were conducted prior to the U.S. Food and Drug Administration (FDA) approval of rituximab; therefore, the assumption of a benefit of rituximab pre-stem cell transplantation (SCT) for FL has been extrapolated from evidence of its use in aggressive non-Hodgkin lymphoma. The lengthy process of conducting and reporting clinical research emphasizes the need to identify surrogate molecular markers that are predictive of long-term survival in FL patients. In addition, further delineation of clinical risk factors may facilitate appropriate selection of follicular lymphoma patients for autologous versus allogeneic SCT.
- A related limitation is that a number of FL studies revealed plateaus on the Kaplan-Meier survival curves, but did not always report how patients were followed-up (passively or actively) or for how long. Retrospective analyses of registry data are good for obtaining long-term follow-up, but patients are heterogeneously treated, whereas randomized controlled trials homogeneously treat patients, but usually present data with shorter follow-up. This differential follow-up could lead to under-reporting of myelodysplastic syndrome/acute myelogenous leukemia incidence, relapse rate, and late mortality.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Feb

Guideline Developer(s)

American Society for Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

National Marrow Donor Program

Guideline Committee

Follicular Lymphoma Review Expert Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: A list of American Society for Blood and Marrow Transplantation (ASBMT) documents, along with links to individual position statements and evidence-based reviews, is available from the ASBMT Web site .

Print copies: Available from Theresa Hahn, PhD, Roswell Park Cancer Institute, Medicine, Elm and Carlton Sts, Buffalo, NY 14263 (e-mail: theresa.hahn@roswellpark.org).

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 1, 2011. The information was verified by the guideline developer on August 15, 2011.

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